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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,451	KAWAI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-13 are pending.

2. Claim 5 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

3. In view of the amendment filed 8/10/06, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 and 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated monomeric protein MP52 comprising *the* amino acid sequence described in SEQ ID NO: 2 or an amino acid sequence described in SEQ ID NO: 2 wherein alanine at position 83 is replaced with a serine, threonine or valine and wherein said monomer protein induces differentiation of osteoblasts measured by promoting alkaline phosphatase activity, **does not** reasonably provide enablement for (1) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity, (2) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid wherein another amino acid is an amino acid selected from the group consisting serine, threonine, alanine and valine, wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity, (3) any monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2 of the Sequence Listing wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity, and (4) *any* agent comprising *any* monomer protein mentioned above in combination with an excipient in sufficient amount to treat or inhibit osteoporosis, osteoarthritis or arthosteitis, bone fracture, a lack of root of teeth and a tooth socket. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the term monomer protein and agent includes numerous members (genus) and variants of TGF-β superfamily having a cysteine related dimmer formation be replaced with another amino acid for "preventing" and treating all diseases affecting bone and/or cartilage.

The specification discloses only one monomer protein comprising *the* amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, wherein the cysteine at position 83 of SEQ ID NO: 2 has been substituted for alanine and wherein the monomer protein induces differentiation of osteoblast by measuring alkaline phosphatase activity (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein mentioned above, the specification does not teach how to make and use *any* monomer protein and *any* agent mentioned above for "preventing" and treating *any and all* diseases affecting bone and/or cartilage without the amino acid sequence.

The specification does not teach which amino acids within the full-length sequence of any and all monomeric protein are critical and can or cannot be change such as substitution, deletion, addition and combination thereof. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo.

It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

Ngo *et al* (PTO 892) teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Mason *et al* (PTO 1449) teach in activin A, a member of the TGFβ superfamily, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), resulting in losses biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and losses of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular).

Given the unlimited number of monomer protein and agent, there is a lack of in vivo working example showing that any undisclosed monomeric protein, particularly the fragment thereof (claim 4) and agent are effective for treating any disease affecting bone and/or cartilage, let alone for "preventing" any and all diseases affecting bone and/or cartilage such as osteoporosis, autoimmune disease such as osteoarthritis or arthrosteitis, any bone fracture, any disease that lacks root of teeth and tooth socket. The actual biological activity and that of the monomer protein, agent and fragment of SEQ ID NO: 2 per se in the bone and/or cartilage remain to be demonstrated. As such, treatment of disease such as autoimmune disease affecting bone and/or cartilage mentioned above using any monomer protein and agent comprising any monomer proteins is highly unpredictable, varies depending on the animal model, means of administration and composition of the monomer protein. Let alone the undisclosed monomer protein, agent and fragment thereof comprising the undisclosed protein is use for "preventing" any and all diseases affecting bone and/or cartilage mentioned above.

Since the structure of the monomer protein is not enabled, any and all agents comprising any undisclosed monomer protein for preventing and treating any disease affecting bone and/or cartilage mentioned above are not enabled.

With regard to monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2, the term "comprising an amino acid sequence" encompasses amino acid sequence that comprise the full-length sequence of SEQ ID NO: 2 or any portion of SEQ ID NO: 2. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 show any biological effect in vitro or in vivo, much less for "preventing" and/or treating any and all diseases affecting bone and/or cartilage mentioned above.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 8/10/06 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended to indicate that the monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity. In addition, applicants point out that a lot of information was present in the state of the art with regard to the dimer MP52 and in particular dimer members of the BMP protein family, which is a subfamily of the TGF-β superfamily. Dimer members of the BMP protein family, including MP52, are characterized by common structural features, thus, changes in activity based on changes in the common structural features, are predictable among these proteins. For example, it was known to a skilled person that the members of this protein family are expressed as precursor proteins from which the mature protein is separated. It was also known that N-terminal ends can be shortened without changing the activity of these mature proteins (WO 89/09788). Thus, one skilled in the art would reasonably expect that fragments of SEQ ID NO: 2, which are shortened at the N-terminus, would have the desired activity. This activity can easily be determined by measuring the differentiation of osteoblast cells by means of the well known alkaline phosphatase assay (ALP). Therefore, the activity was not only expected due to the knowledge of the state of the art, but could also easily be determined. WO 89/09788 (mentioned above) describes structural features and homologies of osteogenic proteins (item 2 of the Abstract) to which the BMP proteins belong, as typical members of the TGF-β superfamily. WO 89/09788 describes how artificial sequences for proteins can be derived which exhibit cartilage and bone activity (item 4 of the Abstract). Examples for artificial sequences, which are derived from the structure of other members of the TGF-I~ family are shown on page 7 at the bottom (COP5, COP7, COP16). In two of these artificial osteogenic proteins, the first 5 amino acids of the 7-cysteine

region are missing, however, they nevertheless retain activity. The derived generic sequences of artificial osteogenic proteins having cartilage and/or bone inducing activity, contain in correspondence with said findings only the conserved 7-cysteine region or are 5 amino acids shorter, i.e. they contain only 6 cysteines (see page 9 and 10 as well as page 24, middle to page 28 at the bottom and claims 3, 4, 5 and 6). However, the cysteine is always retained as an essential feature for dimerization. Thus, it becomes clear that the inventors of WO 89/09788 considered only the conserved 7- or even only 6-cysteine region of this protein family as important for structure and activity. In addition, WO 89/09788 gives information about some amino acids within the conserved cysteine region, which are, according to the inventors of WO 89/09788, in addition to the cysteines, very important for the three-dimensional folding and activity. Page 11 is referenced, wherein it is stated: "Note that these generic sequences have 6 and preferably 7 cysteine residues where inter- or intramolecular disulfide bonds can be formed and contain other critical amino acids influences the tertiary structure of the proteins". In view of this information of the state of the art with regard to dimer proteins a person skilled in the art would assume that monomer proteins could also be shortened at their N-terminus without losing activity. A lot was known with regard to dimer proteins which could easily be transferred to the corresponding monomer protein after the present inventors found that MP52 proteins are active without the intermolecular cysteine bond. Therefore, guidance with regard to amino acids critical for structure and function for the proteins of this family was available in the art and could easily be transferred to the corresponding monomer protein. Applicants also point out that US 5,658,882, states that "the first cysteine in the 7-cysteine structure characteristic of TGF-P proteins begins at nucleotide #577. The last cysteine ends at #879. Thus, it is expected that DNA sequences encoding active BMP-12 species will comprise nucleotides #577 to #879 of SEQ ID NO: 1" (see column 5, lines 60-65). In view of the extensive knowledge in the art at the time the present invention was made, applicants contend that one skilled in the art would be able to make and use the claimed monomer protein.

In response, the specification describes only one specific amino acid sequence isolated from human MP52 comprising *the* amino acid sequence described in SEQ ID NO: 2 or an amino acid sequence described in SEQ ID NO: 2 wherein alanine at position 83 is replaced with a serine, threonine or valine and wherein said monomer protein induces differentiation of osteoblasts measured by promoting alkaline phosphatase activity. According to the specification, the cysteine at position 83 may be substituted for alanine. The specification discloses the cysteine

at position 83 of SEQ ID NO: 2 may be substituted for or other amino acid selected from the group consisting serine, threonine and valine. However, there is no disclosure for the asserted activity in substituting cysteine for serine, threonine or valine.

The specification does not disclose the structure of any monomer protein comprising an amino acid sequence belonging to TGF-β superfamily, of which cysteine related to a dimer formation of the protein has been replaced with any other amino acid and still induces differentiation of osteoblasts as measured by alkaline phosphatase activity other than SEQ ID NO: 2. The differentiation of osteoblasts is merely a sought-after biological activity, without any direction as to how to make such variants having said activity. The specification does not teach how to make the variants in that it only discloses how to test for said activity, once the variant is made. Even assuming arguendo, that one of ordinary skill in the art would start with the disclosed sequence of SEQ ID NO: 2, the term "*an* amino acid sequence" could be the full length of SEQ ID NO: 2, with or without additional amino acids at either or both ends or any or any portion of SEQ ID NO: 2. The specification as filed does not disclose the structure of any and all monomeric protein having a sequence that is *longer* than the length of SEQ ID NO: 2 or any other monmer protein from TGF-β having a cysteine related to dimer formation of the protein replaced with any amino acid wherein the undisclosed monomer still retains activity of differentiating osteoblasts, in turn, effective for treating or inhibiting osteoporosis, treating or inhibiting autoimmune osteoarthritis or arthrosteitis, or treating any bone fracture or lack of root of teeth and tooth socket. There is a lack of guidance as to which amino acids to be added. There is a lack of in vivo working example showing any monomeric protein could treat any diseases.

Likewise, the specification as filed does not disclose the structure of any and all monomeric protein having a sequence that is *shorter* than the length of SEQ ID NO: 2 having a cysteine related to dimer formation of the protein replaced with any amino acid wherein the undisclosed monomer still retains activity of differentiating osteoblasts, in turn, effective for treating or inhibiting osteoporosis, treating or inhibiting autoimmune osteoarthritis or arthrosteitis, or treating any bone fracture or lack of root of teeth and tooth socket. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 of any monomer protein from the TGF-β show any biological effect and useful for preventing and/or treating any disease such as osteoporosis, autoimmune osteoarthritis or arthrosteitis, bone fracture or lack of root of teeth and/or tooth socket. While it may be routine in the art to modify sequence, there must be some guidance as to what modification in which sequence a skilled artisan can make and

still retain the required activity. As such, the specification is merely extending an invitation to one skilled in the art to further experimentation to come up with the structure of the claimed monomeric protein. Given the potentially large number of monomeric protein one could make, the unpredictability in the art and the lack of in vivo working example or guidance in the specification as to the direction in which the experimentation should proceed, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

6. Claims 1-4 and 6-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity, (2) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid wherein another amino acid is an amino acid selected from the group consisting serine, threonine, alanine and valine, wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity, (3) any monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2 of the Sequence Listing wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity, and (4) *any* agent comprising *any* monomer protein mentioned above in combination with an excipient in sufficient amount to treat or inhibit osteoporosis, osteoarthritis or arthosteitis, bone fracture, a lack of root of teeth and a tooth socket.

The scope of the term monomer protein and agent includes numerous members (genus) and variants of TGF-β superfamily having a cysteine related dimmer formation be replaced with another amino acid for "preventing" and treating any disease affecting bone and/or cartilage.

The specification discloses only *one* monomer protein from human MP52 comprising *the* amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, wherein the cysteine at position 83 of SEQ ID NO: 2 has been substituted for alanine and wherein the

monomer protein induces differentiation of osteoblast by measuring alkaline phosphatase activity (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein MP52 from human comprising the amino acid sequence of SEQ ID NO: 2 mentioned above wherein the protein having a cysteine residue at position 83 that related to dimer formation of the protein substituted for alanine and retains differentiation of osteoblast as measured by alkaline phosphatase activity, the structure of any and all other monomer protein or agent comprising any amino acid sequence belonging to TGF-β that induces differentiation of osteoblasts is not adequately described without the amino acid sequence. Further, the term "an amino acid sequence" could be the full length of SEQ ID NO: 2, with or without additional amino acids at either or both ends or any or any portion of SEQ ID NO: 2.

The specification as filed does not disclose the structure of any and all monomeric protein having a sequence that is *longer* than the length of SEQ ID NO: 2 having a cysteine related to dimer formation of the protein replaced with any amino acid wherein the undisclosed monomer still retains activity of differentiating osteoblasts, in turn, effective for treating or inhibiting osteoporosis, treating or inhibiting autoimmune osteoarthritis or arthrosteitis, or treating any bone fracture or lack of root of teeth and tooth socket.

Likewise, the specification as filed does not disclose the structure of any and all monomeric protein having a sequence that is *shorter* than the length of SEQ ID NO: 2 having a cysteine related to dimer formation of the protein replaced with any amino acid wherein the undisclosed monomer still retains activity of differentiating osteoblasts, in turn, effective for treating or inhibiting osteoporosis, treating or inhibiting autoimmune osteoarthritis or arthrosteitis, or treating any bone fracture or lack of root of teeth and tooth socket. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 have been described in the specification as filed. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 show any biological effect and useful for preventing and/or treating any disease such as osteoporosis, autoimmune osteoarthritis or arthrosteitis, bone fracture or lack of root of teeth and/or tooth socket.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself for the biological variants thereof is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 8/10/06 have been fully considered but are not found persuasive.

Applicants' position is that extensive knowledge was available in the art regarding dimer members of the BMP protein family, which is a subfamily of the TGF-13 superfamily. In Falkner v. Inglis, 79 USPQ2d 1001 (CAFC 2006), the essential regions of the sequences were known in the art but not recited in the application. The court held that the application met the requirements for written description since one of ordinary skill in the art would have possessed the required knowledge and a patent need not teach, and preferably omits, what is well known in the art. In the present situation, sequences for dimer members of the TGF-13 superfamily were known in the art as were the regions critical for activity.

In response, The specification discloses only *one* monomer protein from human MP52 comprising *the* amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, wherein the cysteine at position 83 of SEQ ID NO: 2 has been substituted for alanine and wherein the monomer protein induces differentiation of osteoblast by measuring alkaline phosphatase activity (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein MP52 from human comprising the amino acid sequence of SEQ ID NO: 2 mentioned above wherein the protein having a cysteine residue at position 83 that related to dimer formation of the protein substituted for alanine and retains differentiation of osteoblast as measured by alkaline phosphatase activity, the structure of any and all other monomer protein or agent comprising any amino acid sequence belonging to TGF-β that induces differentiation of osteoblasts is not adequately described without the amino acid sequence. Further, the term "an amino acid sequence" could be the full length of SEQ ID NO: 2, with or without additional amino acids at either or both ends or any or any portion of SEQ ID NO: 2.

The specification as filed does not disclose the structure of any and all monomeric protein having a sequence that is *longer* than the length of SEQ ID NO: 2 having a cysteine related to dimer formation of the protein replaced with any amino acid wherein the undisclosed monomer still retains activity of differentiating osteoblasts, in turn, effective for treating or inhibiting osteoporosis, treating or inhibiting autoimmune osteoarthritis or arthrosteitis, or treating any bone fracture or lack of root of teeth and tooth socket.

Likewise, the specification as filed does not disclose the structure of any and all monomeric protein having a sequence that is *shorter* than the length of SEQ ID NO: 2 having a cysteine related to dimer formation of the protein replaced with any amino acid wherein the undisclosed monomer still retains activity of differentiating osteoblasts, in turn, effective for treating or inhibiting osteoporosis, treating or inhibiting autoimmune osteoarthritis or arthrosteitis, or treating any bone fracture or lack of root of teeth and tooth socket. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 have been described in the specification as filed. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 show any biological effect and useful for preventing and/or treating any disease such as osteoporosis, autoimmune osteoarthritis or arthrosteitis, bone fracture or lack of root of teeth and/or tooth socket.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself for the biological variants thereof is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-2 and 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Brunner et al (J Biol Chem 264(23): 13660-13664, 1989; PTO 892).

Brunner et al teach a monomer protein or agent such as transforming growth factor β1 precursor that belongs to the TGF-β superfamily of which cysteine at position 223 and 225 that related to a dimmer formation of the protein has been replaced with another amino acid such as serine (see abstract, page 13661, column 1, Figure 2, in particular). Claims 6-11 are included in this rejection because the agent comprising the same monomer protein. A product is a product, irrespective of it's intended use. The reference monomer protein is associated with an excipient such as 0.2M acetic acid or buffer (see page 13661, col. 1, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/10/06 have been fully considered but are not found persuasive.

Applicants' position is that Brunner is directed to transforming growth factor 131 which inhibits proliferation of a variety of cells, stimulates anchorage independent growth of non tumorigenic fibroblasts, stimulates fibronectin and collagen synthesis and secretion, induces squamous cell differentiation and inhibits myogenic differentiation. Brunner does not suggest or disclose a monomer protein which induces differentiation of osteoblasts as measured by alkaline phosphatase activity.

In response, Brunner et al teach a monomer protein or agent such as transforming growth factor β1 precursor that belongs to the TGF-β superfamily of which cysteine at position 223 and 225 that related to a dimmer formation of the protein has been replaced with another amino acid such as serine (see abstract, page 13661, column 1, Figure 2, in particular). Claims 6-11 are included in this rejection because the agent comprising the same monomer protein. A product is a product, irrespective of it's intended use. The reference monomer protein is associated with an excipient such as 0.2M acetic acid or buffer (see page 13661, col. 1, in particular). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teach the identical chemical structure or amino acid sequence, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Further, Since the Patent Office does not have the facilities for examining and comparing the monomer protein of the instant invention to those of the prior art, the burden is on applicant to

show that the prior art monomer protein is different from the claimed monomer protein. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

9. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated US Pat No 5,658,882 (Aug 19, 1997; PTO 892)

The '882 patent teaches a monomeric polypeptide comprising an amino acid sequence such as Phe Pro Leu Arg Ser His Leu Glu Pro Thr Asn of SEQ ID NO: 6 (see reference SEQ ID NO: 6 residues 15 to 25, which corresponds to residues 53 to 63 of claimed SEQ ID NO: 2, in particular). The term "comprising *an* amino acid sequence" encompasses amino acid sequence that comprises the full-length sequence of SEQ ID NO: 2 or any portion of claimed SEQ ID NO: 2. The '882 patent teaches a portion of claimed SEQ ID NO: 2. Further, the term "comprising" is open-ended. It expands the portion to include additional amino acids at either or both ends to include the reference peptide. The reference peptide inherently is monomeric because the short peptide does not contain the two cysteine residues related to dimmer formation of SEQ ID NO: 2 (cysteine residues 83-84 of claimed SEQ ID NO: 2). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teach the identical chemical structure or amino acid sequence, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/10/06 have been fully considered but are not found persuasive.

Applicants' position is that claim 4 has been amended to depend from claim 1. The fragment disclosed by the patent 5,658,882 (hereinafter '882) does not have biological activity.

In response, claim 4 recites the monomer protein comprising an amino acid sequence described in SEQ ID NO: 2 of the Sequence Listing wherein said monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity. The term "comprising *an* amino acid sequence" encompasses amino acid sequence that comprises the full-length sequence of SEQ ID NO: 2 or any portion of claimed SEQ ID NO: 2. The '882 patent teaches a portion of claimed SEQ ID NO: 2. Further, the term "comprising" is open-ended. It expands the portion to include additional amino acids at either or both ends to include the reference peptide. The reference peptide inherently is monomeric because the short peptide does not contain the two

cysteine residues related to dimmer formation of SEQ ID NO: 2 (cysteine residues 83-84 of claimed SEQ ID NO: 2). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teach the identical chemical structure or amino acid sequence, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, the reference teachings anticipate the claimed invention.

10. Claims 12 and 13 are free of prior art.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
October 27, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600